

in Fig. 5A as issued as well as in the original Fig. 5A as filed.

## '554 Patent - Fig. 5A As Issued

- Three main errors that need correction:
  - LE is incorrect (should be VQ)
  - F in box is incorrect (should be outside)
  - codon for I (ATT) should be ATC

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FIG. 5A

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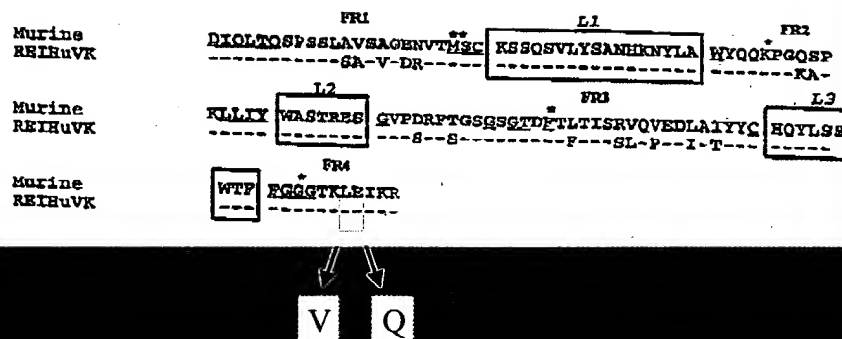
GACATTGAGCTGACCCAGTCTCCATCATCTCTGAGCGCATCTGTTGGAGATAGGGTCACT
1  CTGTAGTCGACTGGGTCAGAGGTAGTAGAGACTCGCGTAGACAACCTCTATCCCAGTGA
  D I O L T Q S P S S L S A S V G D R V T -
61  ATG ATC GTCCAGTCAAAGTGTTTATACAGTGCAAATCACAAGAACTACTTGGCC
  TACTCGACATTCAGGTCAGTTTCACAAAATATGTCAGGTTAGTGTCTTGATGAACCGG
      CDR1
M S C K S S Q S V L Y S A N H K N Y L A -
121 TGGTACCAGCAGAAACCAGGGAAGCACCTAAACTGCTGATCTACTGGGCATCCACTAGG
  ACCATGGTCGTCTTGGTCCCTTCGTGGATTGACGACTAGATGACCCGTAGGTGATCC
      CDR2
W Y Q Q K P G K A P K L L I Y W A S T R -
181 GAATCTGGTGTCCCTTCGCGATTCTCTGGCAGCGGATCTGGGACAGATTTACTTTCACC
  CTTAGACCACAGGGAAGCGCTAAGAGACCGTCGCCTAGACCTGTCTAAAATGAAAGTGS
  E S G V P S R F S G S G S G T D F T F T -
241 ATCAGCTCTCTTCAACCAGAAGACATTGCAACATATTATTGTCACCAATACCTCTCCTCG
  TGGTCTTCTTACCTTATAATAACAGTGGTTATGGAGAGGAGC
  W T F P E V A Q Y Y C H Q Y L S S -
      CDR3
TGGAGTTTCGGTGGAGGGACCAACTGGGATCAACGT
301 ACCTCAAGCCACCTCCCTGGTTCACCTCTAGTTTGCA
  W T F G G G T K L E I K R

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## '554 Patent - Fig. 1A

Fig. 1A.



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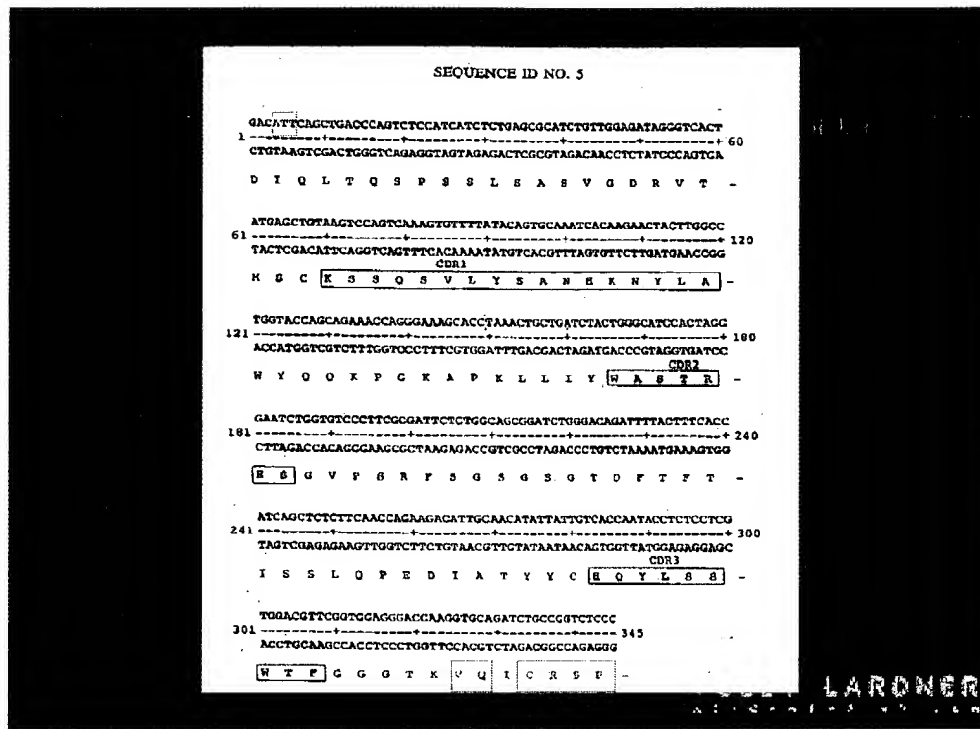
## '554 Patent - Fig. 5A As Filed

- No IKR (instead ICRSP), but changed to IKR during prosecution - argued that Fig. 1 as filed showed IKR
- did have VQ, but changed to LE during prosecution - argued that Fig. 1 as filed showed LE
- did have erroneous I codon (ATT)

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As summarized in the slide immediately above, arguments were made for certain sequence changes based on Fig. 1 during prosecution of the parent patent. The change to IKR was correct, but the change of VQ to LE was incorrect (at the time these arguments were made in the parent patent, LE was thought to be correct). As shown below, however, there are several reasons why one of ordinary skill in the art would have realized that VQ should not have been changed and that IKR was a correct change. In addition, as discussed

at the interview, applicants have made a deposit of the material containing the correct sequence which further supports the changes being made.



## '554 Patent - Support for Changes

- Support for F in FR4 (outside box)
  - ‘554 patent uses “Kabat numbering” (col. 11, line 66; p. 22, line 26)
  - Kabat scheme “always” classifies F as first AA of FR (several citations support this)
- Support for LE → VQ
  - original Fig. 5A, which is the only sequence consistent with oligo SEQ ID 18 (p. 27, line 24, which is SEQ ID 21 in ‘554 patent), the actual primer used to amplify

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The corresponding reference to the “Kabat numbering” is found on page 22, lines 4-13 and lines 25-29 of the specification. Applicants will provide a copy of Kabat shortly under separate cover that discloses that the first amino acid residue of the FR4 is always

“F.” Additionally as noted above, original Fig. 5A contained the “VQ” in FR4 “FGGGTKVQICRSP.” These two amino acid sequences were incorrectly changed to the corresponding murine sequences during prosecution of the ‘554 patent. As noted above, SEQ ID NO:21 (SEQ ID NO:18 as originally filed) supports this sequence.

## ‘554 Patent - Support for Changes

- Oligo SEQ ID NO: 18 (issued SEQ ID NO: 21):

~~CAC~~CGGCAGATCTGCACCTTGGTCCCTCCACCG

G CCA CCT CCC TGG TTC CAC GTC TAG ACG GC~~CA~~

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## ‘554 Patent - Support for Changes

- Oligo SEQ ID NO: 18 (issued SEQ ID NO: 21):

- ~~CAC~~CGGCAGATCTGCACCTTGGTCCCTCCACCG

- this oligo lines up with the bottom strand in reverse direction of Fig. 5A:

- G G G T K V Q I C R

- C GGT GGA GGG ACC AAG GTG CAG ATC TGC CGG TC

- G CCA CCT CCC TGG TTC CAC GTC TAG ACG GC~~CA~~

- underlined sequence shows the BglIII site
- Fig. 5A as filed contains the intermediate PCR product sequence (ICR)

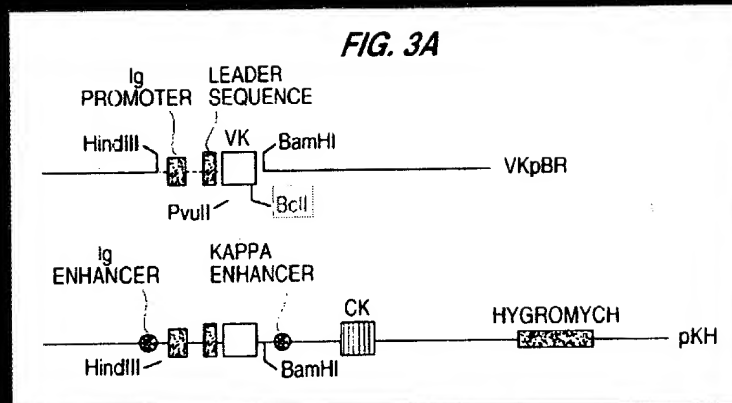
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## '554 Patent - Support for Changes

- Support for IKR & further support for VQ
- BclI site used in staging vector (col. 15, lines 21-26; p. 28, lines 1-6) introduces the first A of K codon & BglIII requires A of Q codon:
  - the previous BglIII cut is depicted as follows:
    - Q I C R S P
    - CA GATC TCC CGG TCT CCC
  - the product to the left of the red line above is then ligated into the BclI site of the staging vector:
    - Q I K R
    - CA GATC AAA CGT

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## '554 Patent - Support for Changes



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## '554 Patent - Support for Changes

- a C (as shown in original Fig. 5A) would be incompatible with use of BclI (codon must start with a T), but a K (as shown in original Fig. 1A) is compatible (codon starts with A)
- one of ordinary skill in the art would resolve the conflict between IKR (original Fig. 1A) and ICRSP (original Fig. 5A) based on the restriction sites & oligo SEQ ID 18 in favor of IKR
- this is not inconsistent with choosing VQ from Fig. 5A because that choice is also dictated by the restriction sites which require Q and oligo SEQ ID 18
- BglII/BclI sites are consistent with the sequence of oligo SEQ ID 18 (issued SEQ ID 21) - anchor for all changes

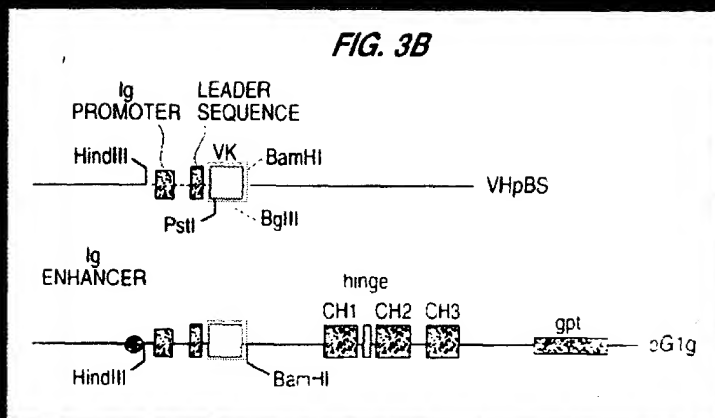
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## '554 Patent - Support for Changes

- Further support comes from Orlandi
- intron removal in expression vector creates final IKR subsequence
  - "The VK and VH sequences for cLL2 or hLL2 can [be] amplified by PCR as described in Orlandi et al. (*Proc. Natl. Acad. Sci., USA*, 86:3833 (1989)) which is incorporated by reference" (col. 8, lines 1-4; p. 15, lines 3-6)
  - Orlandi at p. 3834, right column, lines 6-9, and in Fig. 2 legend cites to Riechmann (*Nature*, 332(1988): 323-327), for explanation of non-coding regions
  - Riechmann (p. 324, legend of Fig. 1), in turn, cites to Hieter (*Cell*, 22(1980): 197-201) for an explanation of "the 3' non-coding sequence taken from a human J<sub>H</sub>-region sequence"

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## '554 Patent - Fig. 3B



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## '554 Patent - Support for Changes

- HindIII/BamHI fragment was subcloned into the expression vector, pK<sub>h</sub>, where it was linked to the genomic DNA for C<sub>k</sub>, including introns and exon:
- ... AAACgt ... ggaacc ... **agCAACTGTC** ...
- ... K ... T V ...
- UPPERCASE, exon; lowercase, intron; Underlined, BamHI site; **bold**, splicing donor and acceptor
- Blue shows the sequence from VKpBR and red shows that from pK<sub>h</sub>. Note that the coding sequences for V<sub>k</sub> and C<sub>k</sub> are discontinued. The stop codon is at the end of C<sub>k</sub> sequence.

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## '554 Patent - Support for Changes

... .. AAACct... ..GCTC... ..AAACCTC... ..

... .. AAACAACTTC... ..

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## '554 Patent - Support for Changes

- After the precursor RNA has been transcribed according to the genome sequence, a splicing event removes the intron sequence and ligates the Vk segment to Ck, resulting in mRNA, which will look like this:

- ... .. AAA CGA ACU CUC... ..

- ... .. K R T V ... ..

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## '554 Patent - Support for Changes

GenBank ACCESSION J00241

AUTHORS Hieber, P.A., Max, E.E., Seidman, J.C., Matzel, J.V. Jr. and Leder, P.  
JOURNAL Cell 22 (1 Pt 1), 197-207 (1980)

Insertion: 1-333

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1  ttctaaactc tgaggggtc ggatgaagtg gccattttt gctaaagca ttgagttac
61  tgcagggtca gaaagcctg caagccctc agaatgggtg caagagctc caacaaaca
121  atttagaac ttattagga ataggggaa gctaggaga aactcaaac atcaagattt
181  taaataagct tcttggtctc ctgtgtataa ttatctgga taagcatgct gttttctgtc
241  tctcaactac atgcccgtg attatacga acaaacacac caaggggag aattttgtta
301  cttaaacacc atctgtctg ctcttttctt cag gctgacaa tctgtcttca
361  tcttccggcc atctggtgag cagtggaaat ctggaactgc ctctgtgtg tgcctgttga
421  ataatctcta tccagagag gccaaagtac agtggaggt ggatarctgc ctcaatctg
481  gtaactcaca ggagagctc acagagcagg acagcaagga cagcaactac agcctcaga
541  gcaactgac gctgagcaaa gcaagctac agaaacacaa agtctacgac tgggaagtca
601  cccatcaggg cctgagctg ccagtcaca acagcttcaa caggggagag tgttagagg
661  agaagcaga ccaactgctc ctggttcaa gctgacccc ctcccatct tggcctctg
721  acccttttcc caaggggac ctacccctat tgggttctc cagctcatct ttcaactac
781  cccctctctc ctcttggct taattatgc taatgttga ggagatgaa taatatagt
841  gatatttgc acctgtggt tctctcttct ctaattttta taattattat ctgttgttta
901  caactacac aattctctt ataagggaat aatatgtag taactctag ggcctctac
961  atttataaa atcaactctc atttatctt accctatcat cctctggaag acagctctc
1021  ctcaaacaca caagcttct gtaactcag tccctgggc cgtggttaga gagattgct
1081  tctttgtttt caactctca gcaagccctc atagctctt ttaagggtga caggtcttca
1141  ggtctatata ctttctctc attcaactg gaatcaaca aggaatttt tcaaacaga
1201  gaaactgc

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As noted by the explanation above, the sequence in FR4, "ICRSP" of the light chain variable region in Fig. 5A represents an intermediate product of the staging vector before insertion into the expression vector, pKH, as shown in Fig. 3A.

## '554 Patent - Support for Fig. 5A

- Support for correction of 1 codon
  - "ATT" should be "ATC" as shown in Riechmann (*Nature*, 332(1988): 323-327, at Fig.1b)
  - Orlandi, however, shows ATT

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The scientific publications that are referred to above will be provided to the Examiner under separate cover.